Comparison between pharmacological, ecological and pollutant control strategies for dengue

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Contents

Dengue

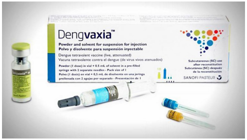
- Mosquito-borne viral infection found in tropical and subtropical regions around the world.
- It occurs in urban and peri-urban areas, with peak transmission during the rainy season.
- Four types of viruses (DENV-1, DENV-2, DENV-3, DENV-4), which transmit through the bite of infected *Aedes aegypti* and *Aedes albopictus* female mosquitoes during the daytime.

Aedes aegypti

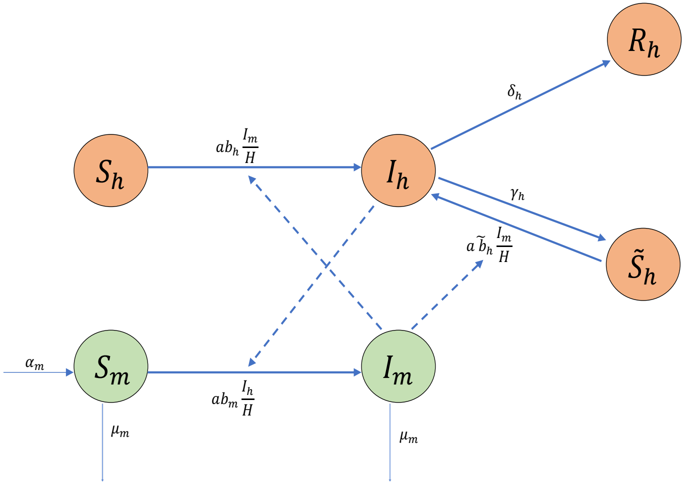
Aedes albopictus

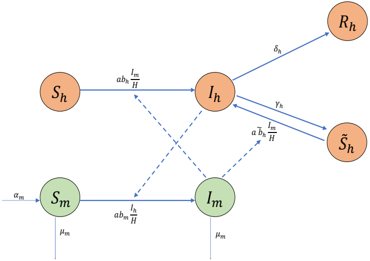
Dengvaxia

- The first commercialized vaccine is CYD-TDV, marketed as dengvaxia by Sanofi Pasteur.
- It was licensed in December 2015 and approved in 11 countries including Philippines.
- It is a live attenuated chimeric product made using recombinant DNA technology by replacing the PrM (pre-membrane) and E (envelope) structural genes of yellow fever attenuated 17D strain vaccine with those from the four dengue serotypes.
- It should be administered in three doses of 0.5 mL subcutaneous (SC) six months apart.
- It is indicated for the prevention of dengue fever caused by dengue virus serotypes 1, 2, 3 and 4 in subjects aged 9 to 45 years with a history of dengue virus infection and living in areas endemic.



Description of Model with Primary and Secondary Susceptible





The dynamics of humans is

$$
\begin{aligned}
S_h'(t) &= -\frac{ab_h I_m(t)}{H(t)} S_h(t) \\
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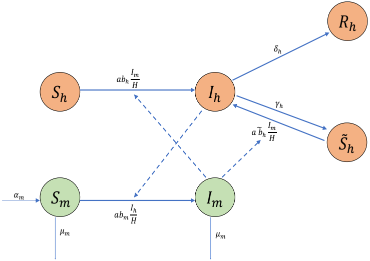

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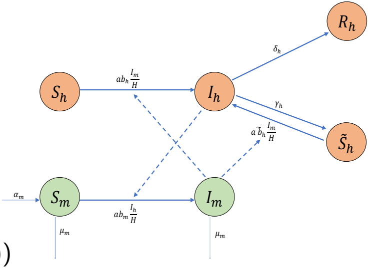
- $H'(t) = 0$



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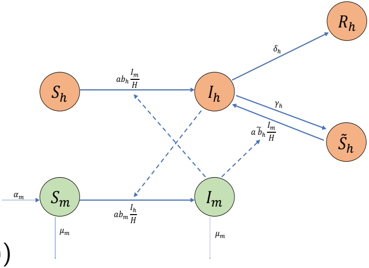

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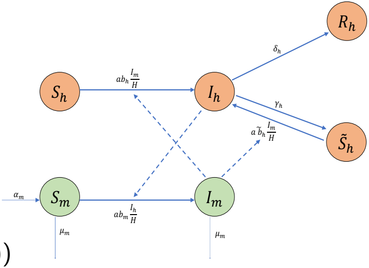
- $M'(t) = (\alpha_m e^{-\beta_m M(t)} - \mu_m)M(t) := g(M)$



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P.-A. Bliman, D. Cardona-Salgado, Y. Dumont, and O. Vasilieva (2019)

Results

Global Well-posedness Theorem

The domain Ω defined by

$$\Omega = \left\{ U \in \mathbb{R}^6_+ : 0 \leq S_h + I_h + \widetilde{S}_h + R_h = H_0, \right.$$
$$\left. 0 \leq S_m + I_m \leq \max\left(\frac{\alpha_m}{\beta_m \mu_m}, M_0\right) \right\} \quad (1)$$

is positively invariant. In particular, for an initial datum in Ω, there exists a unique global in time solution U in $\mathcal{C}(\mathbb{R}_+, \Omega)$.

Disease Free Equilibrium

- $E_1 = (S_h^*, 0, \widetilde{S}_h^*, R_h^*, 0, 0)$
- $E_2 = \left(S_h^*, 0, \widetilde{S}_h^*, R_h^*, \frac{1}{\beta_m} \ln\left(\frac{\alpha_m}{\mu_m}\right), 0\right)$

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- $\mathcal{R}_0 < 1$ where $\mathcal{R}_0 = \sqrt{\frac{a^2 b_m \ln\left(\frac{\alpha_m}{\mu_m}\right)\left(b_h S_h^* + \widetilde{b}_h \widetilde{S}_h^*\right)}{H_0^2 \mu_m \beta_m (\gamma_h + \delta_h)}}$

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Theorem

1. *If $\alpha_m < \mu_m$, then E_1 is globally asymptotically stable.*
2. *If $\alpha_m > \mu_m$ and $\mathcal{R}_0 > 1$, then E_2 is globally asymptotically stable.*

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2. *If $\alpha_m > \mu_m$ and $\mathcal{R}_0 > 1$, then E_2 is globally asymptotically stable.*

The basic reproduction number $\mathcal{R}_0$ has a biological meaning when $\alpha_m > \mu_m$. It means that the average number of new infected humans is proportional to the transmission rate due by biting during the infection period $1/(\gamma_h + \delta_h)$ and mosquitoes life expectancy $1/\mu_m$.

Optimal Control Problem

We consider the objective function

$$\mathcal{J}(w_1, w_3, w_m) = \int_0^T I_h(t) + \frac{1}{2}\left(A_1 w_1^2(t) + A_3 w_3^2(t) + A_m w_m^2(t)\right) dt$$

subject to

$$\begin{aligned}
S_h'(t) &= -\frac{a b_h I_m(t) S_h(t)}{H_0} - w_1(t) S_h(t) \\
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Lemma

There exists an optimal control $w^* = (w_1^*(t), w_3^*(t), w_m^*(t))$ *such that*

$$\mathcal{J}(w_1^*, w_3^*, w_m^*) = \min_{w \in W} \mathcal{J}(w_1, w_3, w_m)$$

under the constraint $(S_h, I_h, \widetilde{S}_h, R_h, S_m, I_m)$ *is a solution of the system.*

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We used the Pontryagin's maximum principle to find the optimal control w^* that minimizes, at each instant t, the Hamiltonian given by

$$\begin{aligned}
\mathcal{H} = {} & \frac{1}{2}\left(I_h + A_1 w_1^2 + A_3 w_3^2 + A_m w_m^2\right) \\
& + \lambda_1\left(-\frac{ab_h I_m S_h}{H_0} - w_1 S_h\right) + \lambda_3\left(\gamma_h I_h - \frac{a\widetilde{b}_h \widetilde{S}_h I_m}{H_0} - w_3 \widetilde{S}_h\right) \\
& + \lambda_2\left(\frac{aI_m\left(b_h S_h + \widetilde{b}_h \widetilde{S}_h\right)}{H_0} - \gamma_h I_h - \delta_h I_h\right) + \lambda_4(\delta_h I_h) \\
& + \lambda_5\left(-\frac{ab_m I_h S_m}{H_0} + g(M) - \mu_m S_m - w_m S_m\right) \\
& + \lambda_6\left(\frac{ab_m I_h S_m}{H_0} - \mu_m I_m - w_m I_m\right).
\end{aligned} \tag{3}$$

Lemma

There exist the adjoint variables $\lambda_i, i = 1, 2, \cdots, 6$ of the system (2) that satisfy the following backward in time system of ODE:

$$
\begin{aligned}
-\frac{d\lambda_1}{dt} &= \lambda_1 \left(\frac{-ab_h I_m}{H_0} - w_1 \right) + \lambda_2 \frac{ab_h I_m}{H_0} \\
-\frac{d\lambda_2}{dt} &= 1 + \lambda_2(-\gamma_h - \delta_h) + \lambda_3 \gamma_h + \lambda_4 \delta_h - \lambda_5 \frac{ab_m S_m}{H_0} + \lambda_6 \frac{ab_m S_m}{H_0} \\
-\frac{d\lambda_3}{dt} &= \lambda_2 \frac{a\widetilde{b}_h I_m}{H_0} + \lambda_3 \left(\frac{-a\widetilde{b}_h I_m}{H_0} - w_3 \right) \\
-\frac{d\lambda_4}{dt} &= 0 \\
-\frac{d\lambda_5}{dt} &= \lambda_5 \left(\frac{-ab_m I_h}{H_0} + \frac{\partial g}{\partial S_m} \right) - \lambda_5(\mu_m + w_m) + \lambda_6 \frac{ab_m I_h}{H_0} \\
-\frac{d\lambda_6}{dt} &= -\lambda_1 \frac{ab_h S_h}{H_0} + \lambda_2 \frac{ab_h S_h + a\widetilde{b}_h \widetilde{S}_h}{H_0} - \lambda_3 \frac{a\widetilde{b}_h \widetilde{S}_h}{H_0} + \lambda_5 \frac{\partial g}{\partial I_m} - \lambda_6(\mu_m + w_m)
\end{aligned}
$$

with the transversality condition $\lambda(T) = 0$.

Theorem

The optimal control variables are given by

$$w_1^*(t) = \max\left(0, \min\left(\frac{\lambda_1 S_h}{A_1}, w_H\right)\right)$$

$$w_3^*(t) = \max\left(0, \min\left(\frac{\lambda_3 \widetilde{S}_h}{A_3}, w_H\right)\right)$$

$$w_m^*(t) = \max\left(0, \min\left(\frac{\lambda_5 S_m + \lambda_6 I_m}{A_m}, w_M\right)\right)$$

Numerical Simulation of Optimal Control

The parameters are taken from Indonesia. (Braselton, Iurii. [2015].)

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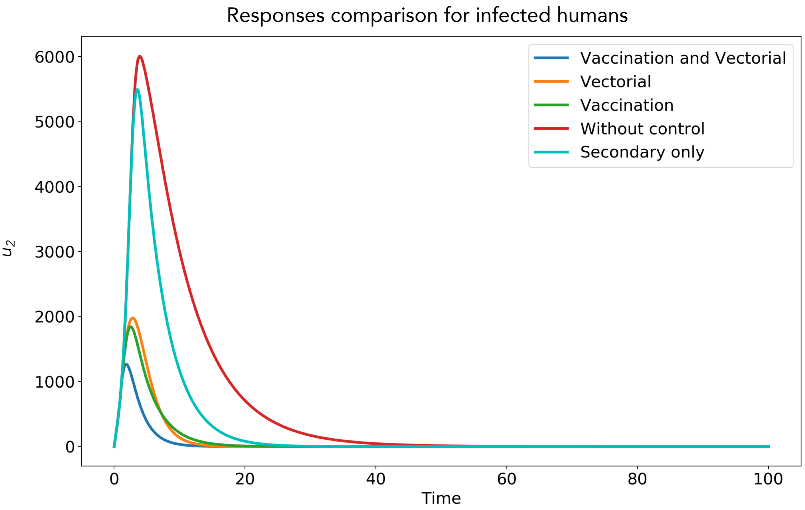
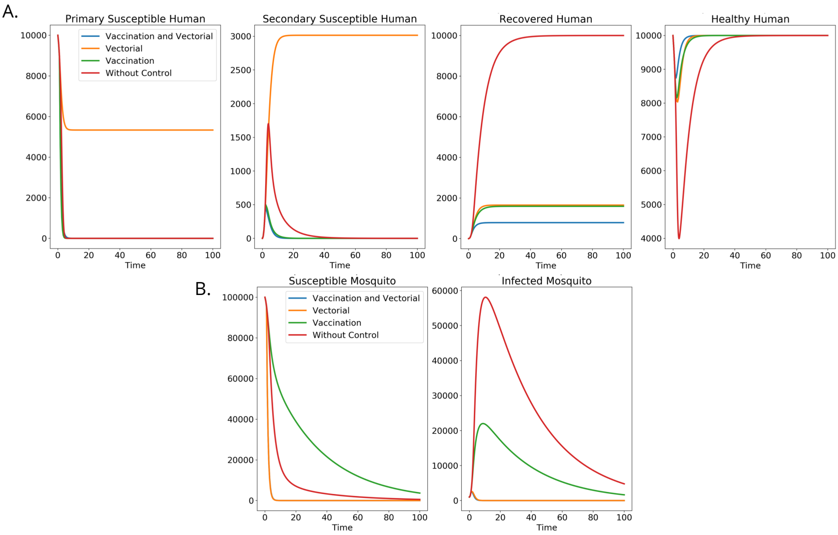
We compare vaccination, vector control, and the combination.

Algorithm 2 Computation of optimal control of dengue-dengvaxia model

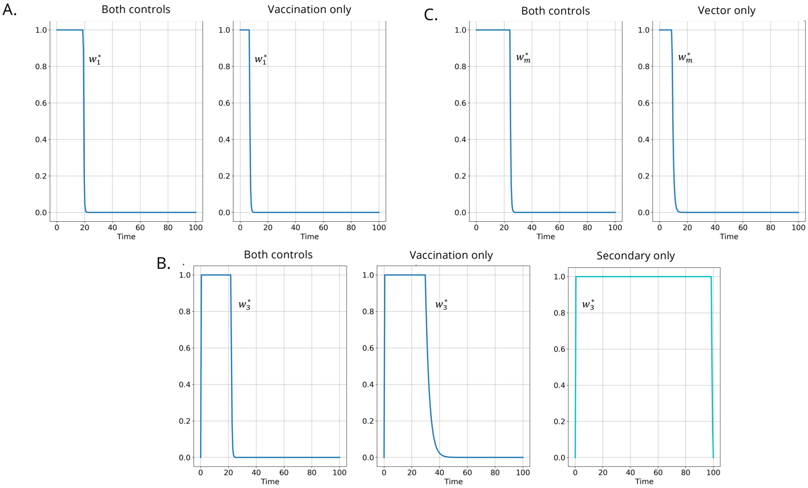
Given $U^0 = (10^4, 0, 0, 0, 10^5, 10^3)$ as initial datum , a final time $T > 0$ and a tolerance $\varepsilon > 0$.
Let w_1^0, w_2^0, w_m^0 randomly chosen following $\mathcal{N}(0, 1)$.
while $||\nabla\mathcal{H}(w^n, U^n, \lambda^n)|| > \varepsilon$, **do**
  solve the forward system u^n,
  solve the backward system λ^n,
  update w^n
  solve the gradient $\nabla\mathcal{H}(w^n, U^n, \lambda^n)$
end while
$w^* = w^n$.

Results


Responses comparison for infected humans
6000
5000
4000
3000
2000
1000
0
u_2
0
20
40
60
80
100
Time
Vaccination and Vectorial
Vectorial
Vaccination
Without control
Secondary only


A.
Primary Susceptible Human
Secondary Susceptible Human
Recovered Human
Healthy Human
Vaccination and Vectorial
Vectorial
Vaccination
Without Control
Time
B.
Susceptible Mosquito
Infected Mosquito
Vaccination and Vectorial
Vectorial
Vaccination
Without Control
Time

Optimal control



Accounting the Life Cycle of Mosquito

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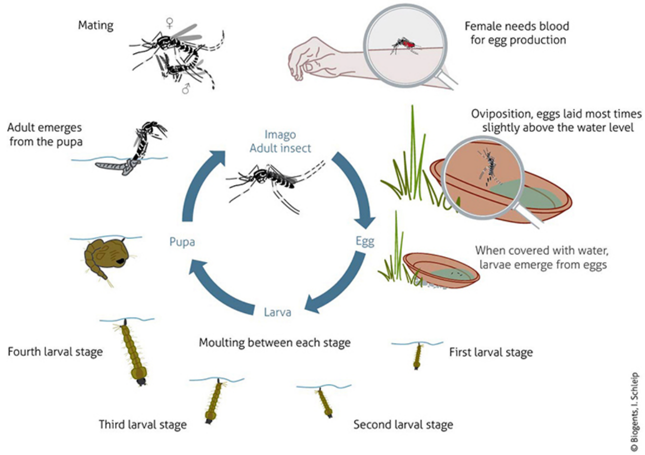
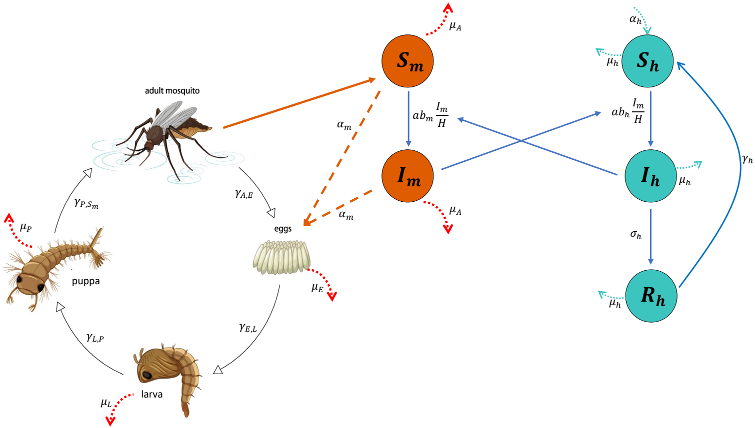


Figura 1: Life cycle of Aedes mosquitoes.

Accounting the Life Cycle of Mosquito



Governing Equation

The equation that governs the dynamics of the metamorphosis of mosquito population is

$$
\begin{aligned}
E'(t) &= \alpha_m(S_m(t) + I_m(t)) - \gamma_{E,L}E(t) - \mu_E E(t) \\
L'(t) &= \gamma_{E,L}E(t) - \gamma_{L,P}L(t) - \mu_L L(t) \\
P'(t) &= \gamma_{L,P}L(t) - \gamma_{P,S_m}P(t) - \mu_P P(t)
\end{aligned}
$$

for young mosquito

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\end{aligned}
$$

for young mosquito and of the adult mosquito is

$$
\begin{aligned}
S_m'(t) &= \gamma_{P,S_m}P(t) - \mu_A S_m(t) - ab_m I_h(t)S_m(t) \\
I_m'(t) &= ab_m I_h(t)S_m(t) - \mu_A I_m(t)
\end{aligned}
$$

with total population of $M_A = S_m + I_m$, $M_Y = E + L + P$

Control Strategy

Copepode

Pesticide

Control Strategy

Copepode

Pesticide

Control Strategy

Copepode

Copepods are natural enemies of the first and second instar of mosquito larvae. Large sized cyclopoid copepods act as predators of mosquito larvae which strongly influence the mosquito larval population.

Pesticide

Control Strategy

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Copepods are natural enemies of the first and second instar of mosquito larvae. Large sized cyclopoid copepods act as predators of mosquito larvae which strongly influence the mosquito larval population.

Pesticide

Space Spraying or Fogging

Control Strategy

- Copepode

$$L'(t) = \gamma_{E,L}E(t) - \gamma_{L,P}L(t) - \mu_L L(t)$$

Control Strategy

- Copepode

$$L'(t) = \gamma_{E,L}E(t) - \gamma_{L,P}L(t) - \mu_L L(t) - w_Y L(t)$$

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Control Strategy

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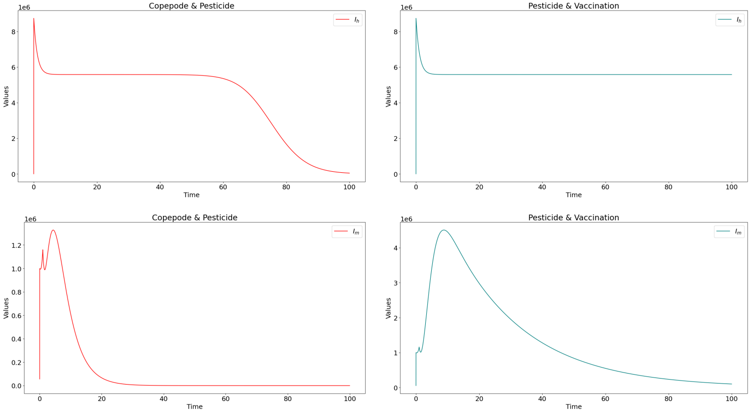
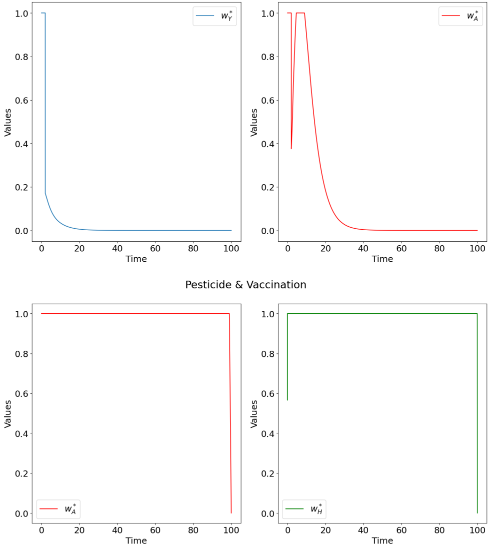
Optimal Solutions of the Infected Human



Optimal Control



Dengue Model with Spatial Distribution

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Diffusion coefficient

$$D(x, y) = D_{min} + \alpha \mathcal{F}_l(x, y) + \beta \mathcal{F}_f(x, y) \quad (4)$$

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- D_{min} as the minimal diffusion value in the absence of resources perception
- $\mathcal{F}_l(x,y)$ and $\mathcal{F}_f(x,y)$ as the dispersion kernels that covered the entire landscape of the involved resources
- α and β are coefficients used to weight the differential impact of resources on the diffusion intensity

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with

$$K_f(d) = e^{-c_f d}$$

$$K_l(d) = e^{-c_l d}$$

Dengue Model with Spatial Distribution

Defining the population density of adults mosquito for every $(x, y) \in \Omega$ and we have

$$\frac{\partial S_m(t,x,y)}{\partial t} = \gamma_{P,S_m} P(t,x,y) - \mu_A S_m(t,x,y) - ab_m I_h(t,x,y) S_m(t,x,y) + D(x,y)\Delta S_m(t,x,y) \quad (6)$$

$$\frac{\partial I_m(t,x,y)}{\partial t} = ab_m I_h(t,x,y) S_m(t,x,y) - \mu_A I_m(t,x,y) + D(x,y)\Delta I_m(t,x,y) \quad (7)$$

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Theorem: Global Well-posedness

Let $0 \leq S_{h,0}, I_{h,0}, R_{h,0} \leq H_0$ and $0 \leq E_0, L_0, P_0 \leq M_{Y,0}$, $0 \leq S_{m,0}, I_{m,0} \leq M_{A,0}$ where $H_0, M_{Y,0}$ and $M_{A,0}$ are the initial population density for human, young mosquito and adult mosquito population, respectively. Then there exists a unique global in time weak solution $U \in L^\infty(\mathbb{R}_+, L^\infty(\Omega))^8$, of the initial boundary value problem. Moreover, the solution is nonnegative, $S_h + I_h \leq H_0$ and $E + L + P \leq M_{Y,0}$ $S_m + I_m \leq M_{A,0}$.

Optimal Control of the Dengue Model with Spatial Distribution

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$$\underset{w}{\text{minimize}}\ \mathcal{J}(U,w) \text{ where } \mathcal{J}(U,w) = \int_\Omega \int_0^T f(U,w,(x,t))dtdX$$

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subject to

$$h(U,\dot{U},w,(x,t)) = 0$$

$$g(U(0),w) = (E_0, L_0, P_0, S_{m,0}, I_{m,0}, S_{h,0}, I_{h,0}, R_{h,0})$$

There exists the adjoint variables λ_i, $i = 1, 2, \cdots, 6$ that satisfy the following backward in time system of partial differential equations

$$-\frac{d\lambda_1(x,t)}{dt} = \lambda_1(x,t)\mu_E + (\lambda_1(x,t) - \lambda_2(x,t))\gamma_{E,L}$$
$$-\frac{d\lambda_2(x,t)}{dt} = \lambda_2(x,t)(\mu_L + w_Y) + (\lambda_2(x,t) - \lambda_3(x,t))\gamma_{L,P}$$
$$-\frac{d\lambda_3(x,t)}{dt} = \lambda_3(x,t)\mu_P + (\lambda_3(x,t) - \lambda_4(x,t))\gamma_{P,S_m}$$
$$-\frac{\partial\lambda_4(x,t)}{\partial t} - D\Delta\lambda_4 = -\lambda_1(x,t)\alpha_m + \lambda_4(x,t)(\mu_A + w_A) + (\lambda_4(x,t) - \lambda_5(x,t))ab_m I_h(x,t)$$
$$-\frac{\partial\lambda_5(x,t)}{\partial t} - D\Delta\lambda_5 = -\lambda_1(x,t)\alpha_m + \lambda_5(x,t)(\mu_A + w_A) + (\lambda_6(x,t) - \lambda_7(x,t))ab_h S_h(x,t)$$
$$-\frac{d\lambda_6(x,t)}{dt} = \lambda_6(x,t)w_H + (\lambda_6(x,t) - \lambda_7(x,t))ab_h I_m(x,t)$$
$$-\frac{d\lambda_7(x,t)}{dt} = 1 + (\lambda_7(x,t) - \lambda_8(x,t))\sigma_h + (\lambda_4(x,t) - \lambda_5(x,t))ab_m S_m(x,t)$$
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-\frac{\partial\lambda_5(x,t)}{\partial t} - D\Delta\lambda_5 &= -\lambda_1(x,t)\alpha_m + \lambda_5(x,t)(\mu_A + w_A) + (\lambda_6(x,t) - \lambda_7(x,t))ab_h S_h(x,t) \\
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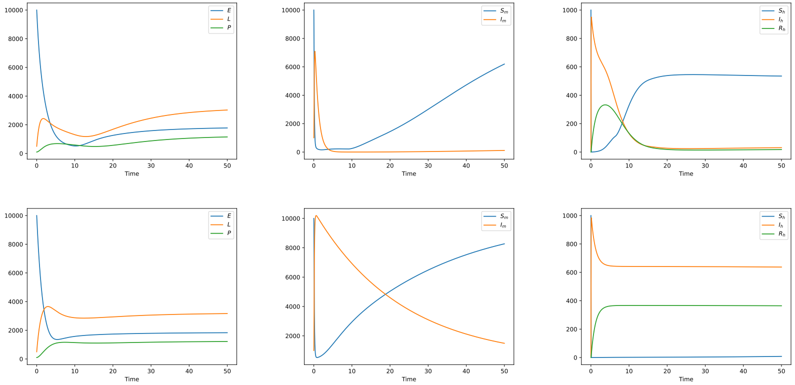
with the transversality condition $\lambda^T(x,T) = 0$ and boundary conditions $\mu^T = \frac{\lambda^T(x,0)h(U(x,0)}{g(U(x,0),w)}$ and $\left.\frac{\partial\lambda(x,t)}{\partial x}\right|_{\partial\Omega} = \left.\frac{\partial U(x,t)}{\partial x}\right|_{\partial\Omega} = 0.$

Optimal Control of the Dengue Model with Spatial Distribution

Furthermore, the optimal control variable w^* is defined as

$$
\begin{aligned}
w_Y^*(t) &= \max\left(0, \min\left(\frac{\lambda_2 L}{-A_Y}, w_M\right)\right) \\
w_A^*(t) &= \max\left(0, \min\left(\frac{(\lambda_4 I_h + \lambda_5 S_h)}{-A_A}, w_M\right)\right) \\
w_H^*(t) &= \max\left(0, \min\left(\frac{\lambda_6 S_h}{-A_H}, w_H\right)\right).
\end{aligned}
$$

Numerical Simulation of the Model with Spatial Distribution



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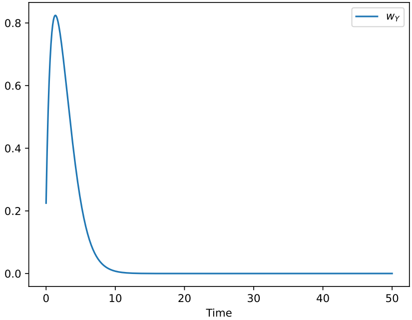

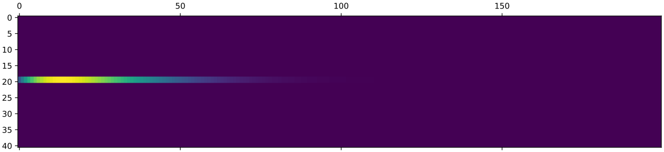

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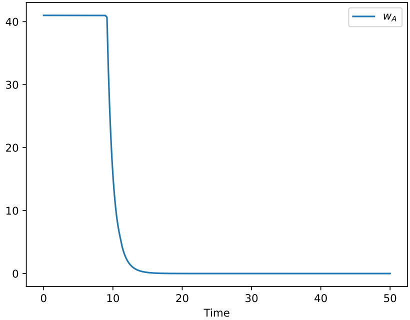

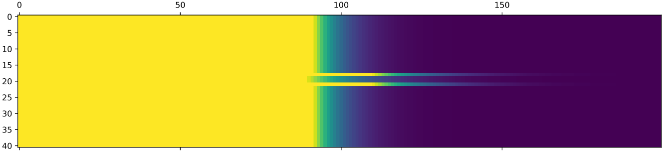

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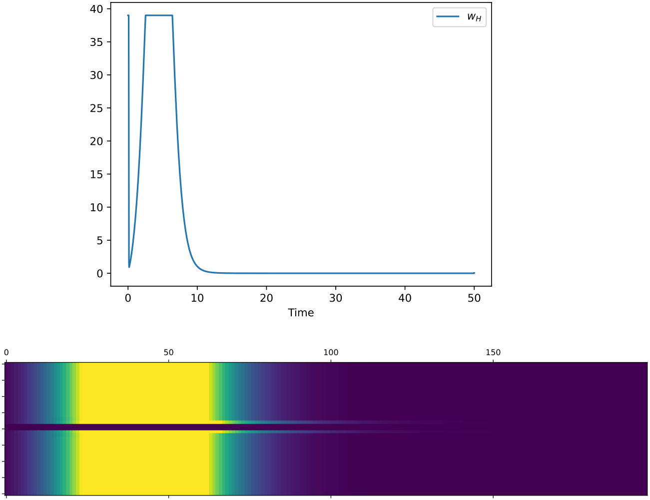

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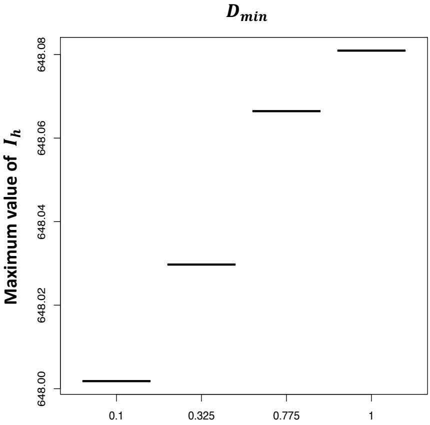
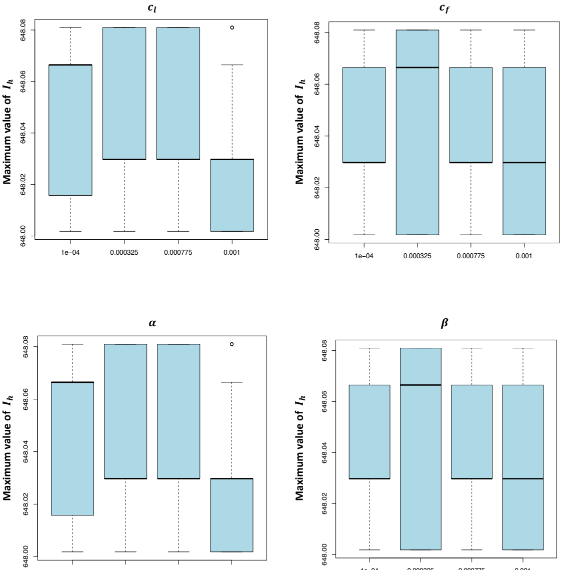
Thank you for your attention!

Sensitivity Analysis

We compute the maximum number of infected humans by varying D_{min} between 0.1 to 1, c_f, c_l, α and β between 10^{-4} to 10^{-3}.




c_l
c_f
α
β
Maximum value of I_h
648.00
648.02
648.04
648.06
648.08
1e−04
0.000325
0.000775
0.001